
بسم الله الرحمن الرحيم

KIDNEY DYSFUNCTION IN HEART FAILURE: CORE CURRICULUM 2025

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آبان 1404

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INTRODUCTION

Pathophysiology of heart failure (HF) with kidney dysfunction

- Maladaptive bidirectional pathways wherein acute or chronic dysfunction of one organ drives acute or chronic dysfunction. hemodynamic, neurohormonal, andinflammatory axes.

- Suboptimal decongestion, diuretic resistance, and low use rates of guideline-directed medical therapy (GDMT)inflammatory axes. high rates of death, hospitalizations for HF, decline in kidney function, and poor quality of life.

WORSENING KIDNEY FUNCTION IN HF

Patient Profile and Chief Complaint	48-y woman-dyspnea and leg swelling during the past month
PMH	CAD, HTN, DM
PDH	aspirin, rosuvastatin, metformin, hydrochlorothiazide, and losartan
Vital sign	T: 36.7C, PR:105, RR:24, BP:160/90
Ph/E	JVP distension, bilateral crackles, soft systolic Murmur cardiac apex pitting edema with warm ex-termites.
Lab Data	NA :133 mEq/L, K :4.0 mEq/L, CL:90 mEq/L, CR:1.7 mg/dL (baseline, 0.8 mg) SUN; 40 mg/dL,s NT-proBNP: 3,000 pg/mL. u/a: trace alb, 1-2 rbc / hpf, SG1020
Echo	EF: 55% No PE

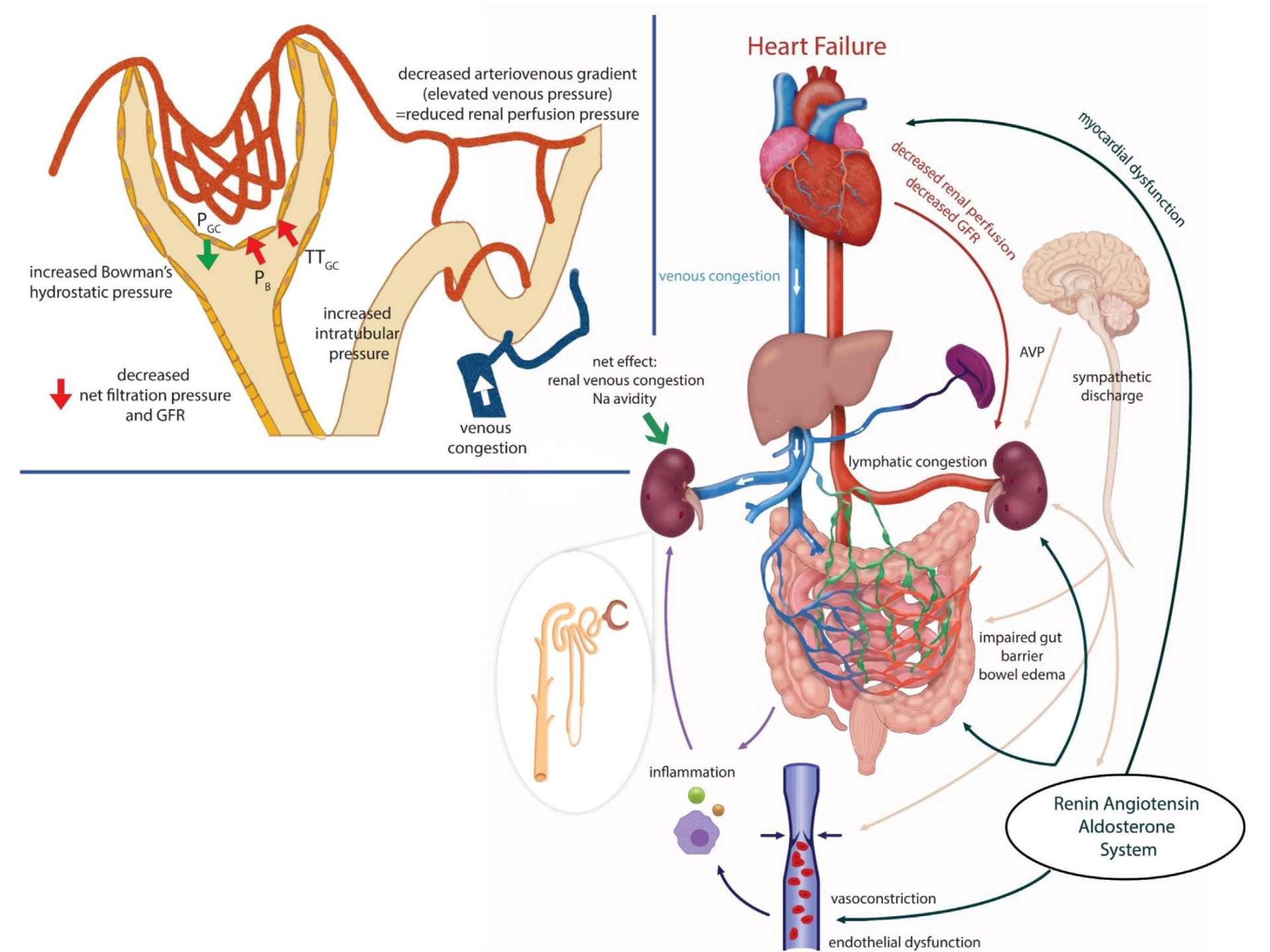
WORSENING KIDNEY FUNCTION IN HF

Question 1: What is the major mechanism behind this patient's worsening kidney function?

(a) Kidney venous congestion
(b) Low cardiac output
(c) Prerenal azotemia
(d) Acute tubular injury
(e) Use of an angiotensin receptor blocker (ARB)

Acute HF ➡ kidney hypoperfusion ➡ neurohormonal activation (RAAS and SNS) ➡ sodium avidity and worsening congestion

Kidney perfusion pressure: difference between mean arterial pressure and central venous pressure (ideally >60 mm Hg)


decreased arteriovenous gradient
(elevated venous pressure)
=reduced renal perfusion pressure
P_{GC}
P_B
TT_{GC}
increased Bowman's
hydrostatic pressure
increased
intratubular
pressure
decreased
net filtration pressure
and GFR
venous
congestion
net effect:
renal venous congestion
Na avidity
Heart Failure
venous congestion
decreased renal perfusion
decreased GFR
myocardial dysfunction
AVP
sympathetic
discharge
lymphatic congestion
impaired gut
barrier
bowel edema
inflammation
Renin Angiotensin
Aldosterone
System
vasoconstriction
endothelial dysfunction

DETERMINING DIURETIC RESPONSE

Patient Profile	56-year-old man
PMH	AF, HTN
PDH	valsartan, carvedilol, spironolactone, apixaban, and furosemide (40 mg/d orally)
Vital sign	T: 36.7C, PR:110, RR: 24, BP:120/80
Ph/E	JVP distension, bilateral crackles, irregularly irregular rhythm, 2+ pitting edema.
Lab Data	NA :135 mEq/L, K :3.6 mEq/L, CL:92 mEq/L, CR:1.3 mg/dL (baseline, 0.8 mg) SUN; 15 mg/dL,s NT-proBNP: 3,500 pg/mL (Dischrage 900).
Echo	EF 30%

DETERMINING DIURETIC RESPONSE

Question 2: What is the most appropriate starting dose for diuretic agents in this patient on admission?

(a) Furosemide 40 mg intravenously
(b) Furosemide 80 mg orally
(c) Bumetanide 1 mg intravenously
(d) Torsemide 40 mg orally
(e) Furosemide 100 mg intravenously

DETERMINING DIURETIC RESPONSE

- Intravenous loop diuretic therapy with at least twice the daily home dose for treatment of acute HF
- No differences between continuous intravenous loop diuretic agent infusion and bolus intermittent dosing.
- Intestinal edema, leading to unpredictable absorption of oral diuretic agents.
- Torsemide and bumetanide exhibiting greater oral bioavailability
- No significant difference in all-cause mortality between torsemide and furosemide
- Modulation of the RAAS for torsemide
- A dose of 40 mg of intravenous furosemide is equivalent to 1 mg of bumetanide or 20 mg of torsemide
- recent data from TRANSFORM suggest a 4:1 ratio between furosemide and torsemide doses

DETERMINING DIURETIC RESPONSE

Question 3: What is the best way to accurately assess diuretic response during decongestion for hospitalized HF?

(a) Daily measurement of patient weight

(b) Urine sodium concentration measured 2 hours after diuretic administration

(c) Charted 24-hour urine output

(d) Clinical signs and symptoms assessed at the bedside

(e) Trend in serum urea nitrogen and creatinine levels

- A spot urine sodium concentration <50-70 mEq/L at 2 hours after loop diuretic agent administration or an hourly urine output <100-150 mL during the first 6 hours denotes an insufficient diuretic response.

- Detector of early (within 24-72 hours) insufficient diuretic response. Use later to be limited as a result of rapid tubular adaptation

DIURETIC RESISTANCE AND ENHANCED DECONGESTIVE

Patient Profile and Chief Complaint	53-year-old woman and HF exacerbation
PMH	DM, CKD (G4A3), HTN, HFPEF
PDH	lisinopril, metoprolol succinate, dapagliflozin, and torsemide (80 mg) daily
Vital sign	T: 36.7C, PR:80, RR: 24, BP:110/70
Lab Data	NA :132 mEq/L, K :4.5 mEq/L, CL:92 mEq/L, CR:3.1 mg/dL (at baseline) SUN; 55 mg/dL,s NT-proBNP: 5000 pg/mL.
Echo	EF 55%
Management	IV furosemide 200 mg twice daily, but, during the first 24 h, the net I/O status is +300 mL. No weight change. The patient continues to receive 4-6 L of oxygen

DIURETIC RESISTANCE AND ENHANCED DECONGESTIVE

Question 4: What is the next best step for this patient?

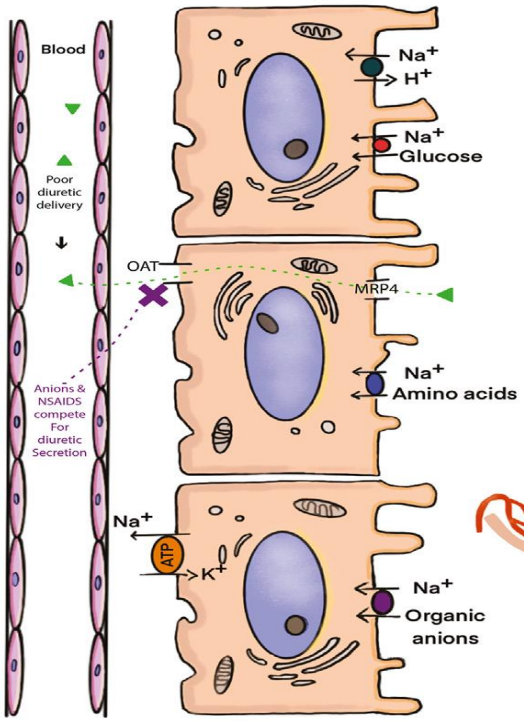
(a) Increase furosemide to 400 mg intravenously twice daily
(b) Change diuretic agent to bumetanide 4 mg intravenously twice daily
(c) Add metolazone 5 mg/d
(d) Discontinue lisinopril treatment
(e) Initiate ultrafiltration

- Diuretic efficiency: which refers to the net fluid lost/urine output per milligram of loop diuretic agent (usually in per–40-mg furosemide dose equivalents

- Diuretic resistance: defined as the attenuation of the maximal diuretic effect that ultimately limits sodium and chloride excretion poor outcomes such as worsening kidney function, recurrent HF hospitalizations, and mortality.

DIURETIC RESISTANCE AND ENHANCED DECONGESTIVE

- Advanced CKD diminished filtered load of sodium nephron
- Diuretic braking phenomen :remodeling, DT hypertrophy that increases distal sodium reabsorption ,aldosterone triggered responses in CDT with increased ENAC mediated reabsorption of sodium.
- Accumulation of organic anions that compete for diuretic secretion in the PCT
- Hypochloremia and metabolic alkalosis both antagonize the effects of loop diuretic agents (Pendrin is a chloride-bicarbonate anion exchanger located in the collecting ducts)



Proximal tubule

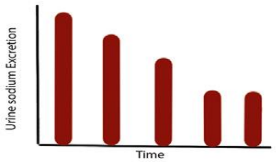
Tubular lumen

Albumin binds

Diuretics

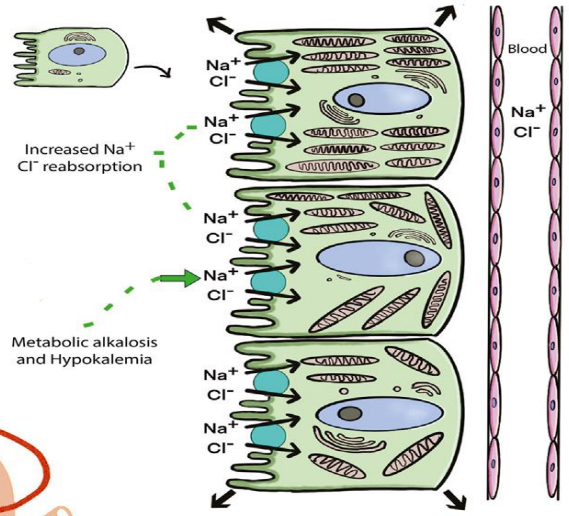
Distal tubule

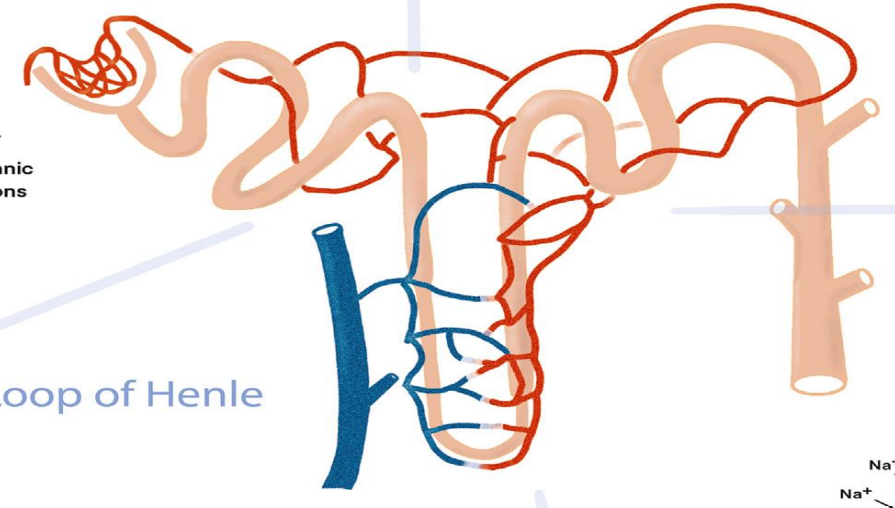
Diuretic Braking Phenomenon



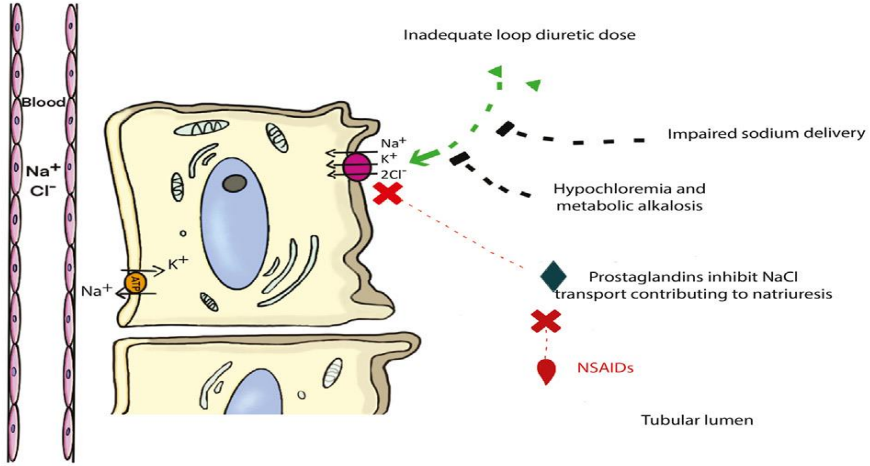
Tubular lumen

Distal tubular hypertro-phy and hyperplasia

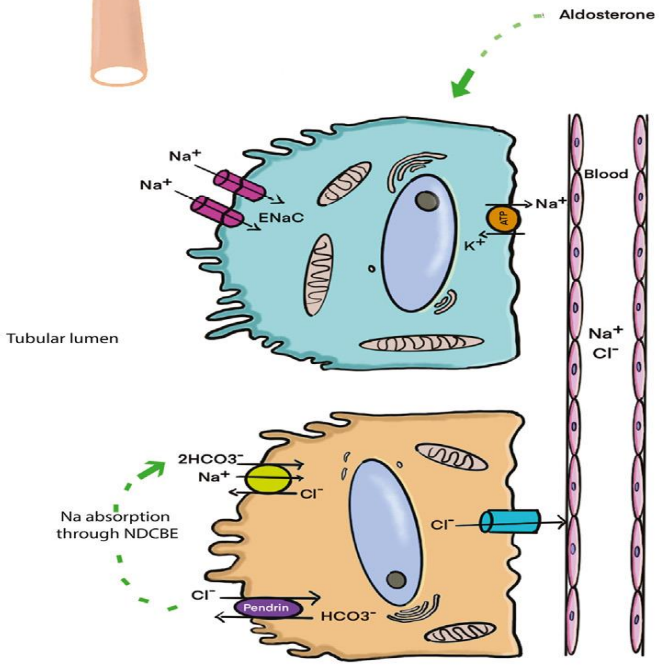




Loop of Henle



Collecting duct



DIURETIC RESISTANCE AND ENHANCED DECONGESTIVE

Table 1. Agents Used for Sequential Nephron Blockade

Site/Agent	Landmark Trial	Relief of Congestion	Clinical Outcomes Benefit
Proximal tubule			
Acetazolamide	ADVOR	Yes	No
SGLT2 inhibitor	EMPULSE	Yes	Yes
Distal tubule			
Thiazide	CLOROTIC	Yes	No
Collecting duct			
MRA	ATHENA-HF	Yes	No
Tolvaptan	EVEREST	Yes	No

Abbreviations: MRA, mineralocorticoid receptor blocker; SGL2, sodium/glucose cotransporter 2.

PROGRESSIVE WORSENING OF KIDNEY FUNCTION AND INADEQUATE RESPONSE TO DECONGESTION

Chief Complaint	**60-year-old man**
PMH	DM, CKD, HTN, AF
PDH	Furosemide 80 mg twice daily, apixaban, and metoprolol succinate
Vital sign	T: 36.7C, PR:120, RR: 22, BP:90/60, O2Sat: 94% with Nasal Oxygen
Lab Data	NA :130 mEq/L K :4.5 mEq/L, CL:89 mEq/L, CR:2.4 mg/dL (at baseline) SUN; 60 mg/dL,s NT-proBNP: 5000 pg/mL.
Echo	EF 25%
Management	IV furosemide 200 mg BID, with intravenous chlorothiazide 500 mg. After the first 24 hours, urine output was 1,500 mL, which was a net negative I/O of −300 mL. No weight change. In the next day, 24-h urine output was reduced to 1,000 mL, CR= 3.2, HCO3= 26, Lactate= 4 mMol/Lit.

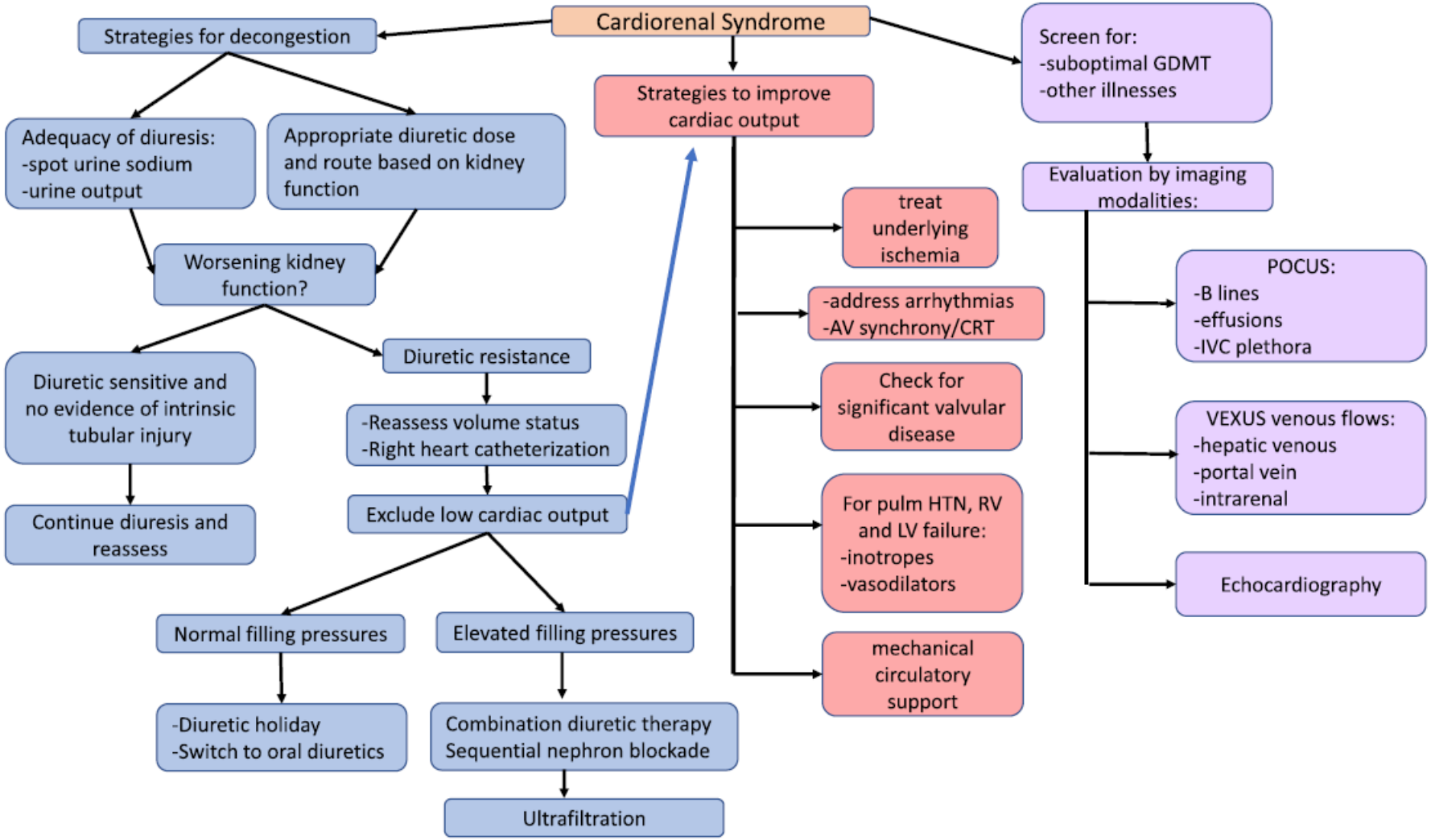
PROGRESSIVE WORSENING OF KIDNEY FUNCTION AND INADEQUATE RESPONSE TO DECONGESTION

Question 5: What is the next best step for this patient?

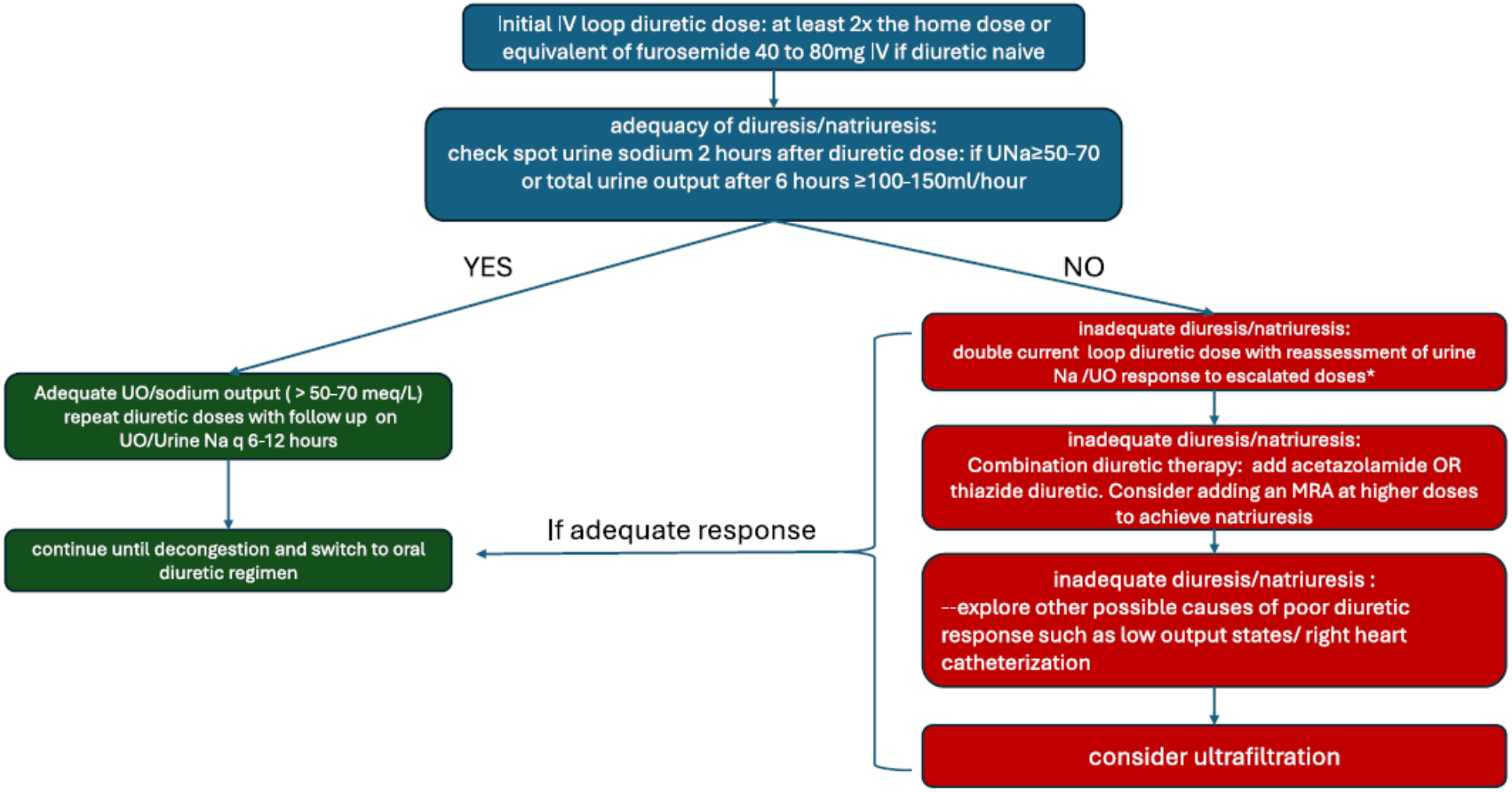
(a) Change to furosemide continuous infusion and add acetazolamide
(b) Change furosemide to bumetanide infusion
(c) Add metolazone 30 minutes before furosemide
(d) Arrange for right heart catheterization
(e) Initiate ultrafiltration

PROGRESSIVE WORSENING OF KIDNEY FUNCTION AND INADEQUATE RESPONSE TO DECONGESTION

Guideline Directed Medical Therapy



PROGRESSIVE WORSENING OF KIDNEY FUNCTION AND INADEQUATE RESPONSE TO DECONGESTION



GDMT OPTIMIZATION IN HF AND KIDNEY DISEASE

Patient Profile And Chief Complain	**63-year-old woman volume overload with worsening kidney functionn**
PMH	DM, CKD(G3aA1),
PDH	Furosemide 40 mg daily, carvedilol
Vital sign	T: 36.7C, PR:120, RR: 22, BP:90/60, O2Sat: 94% with Nasal Oxygen
Lab Data	NA :130 mEq/L K :4.5 mEq/L, CL:89 mEq/L, CR:2.4 mg/dL (at baseline) SUN; 60 mg/dL,s NT-proBNP: 5000 pg/mL.
Echo	EF30%
Management	During admission, she received loop diuretic agents, her kidney function returned to preadmission measurements, and she regained her dry weight of 215 lbs

GDMT OPTIMIZATION IN HF AND KIDNEY DISEASE

Question 7: What additional classes of agents constitute GDMT for this individual?

(a) Angiotensin receptor/neprilysin (ARN) inhibitors, sodium/glucose cotransporter 2 (SGLT2) inhibitors

(b) ARN inhibitors, SGLT2 inhibitors, mineralocorticoid receptor antagonists (MRAs)

(c) ARN inhibitors, MRAs

- The ARN inhibitor sacubitril/valsartan clinical benefits in cardiovascular and/or kidney outcomes
- Neprilysin is an endopeptidase that cleaves a variety of peptides (natriuretic peptides, bradykinin, adrenomedullin, substance P, angiotensin I and II, and endothelin).

GDMT OPTIMIZATION IN HF AND KIDNEY DISEASE

- Role of ARN inh in several cardiovascular, kidney, pulmonary, gastrointestinal, endocrine, and neurologic functions.
- Increase vasodilatory natriuretic peptides and prevent activation of the RAAS.
- lower eGFR slope decline and decreased HF-related hospitalizations compared with valsartan alone.
- Reduced cardiovascular and all-cause mortality in HFrEF versus enalapril.
- Increased albuminuria (asodilation of the afferent arteriole and a relative vasoconstriction of the efferent arteriole).

GDMT OPTIMIZATION IN HF AND KIDNEY DISEASE

- Steroidal MRAs in HFrEF but remain underused, especially in patients with advanced CKD.
- Preserved EF, spironolactone was not shown to be beneficial in improving clinical outcomes.
- Nonsteroidal MRA finerenone equal distribution between heart and kidney tissues, a shorter half-life, higher MR selectivity and affinity, and lower rates of hyperkalemia.
- β-Adrenergic receptor blockers in HFrEF are used widely across the range of CKD stages.

GDMT OPTIMIZATION IN HF AND KIDNEY DISEASE

- SGLT2 inhibitor agents have been shown to have multiple cardiac/kidney protective effects improved cardiac metabolism, reduced oxidative stress, modulation of neurohormonal pathways, attenuation of myocardial inflammation, and preservation of endothelial function.

- SGLT2 inhibitors are generally safely initiated for patients with an eGFR ≥20 mL/min/1.73 m2; as kidney function progressively worsens, SGLT2 inhibitors can be continued until the initiation of dialysis and/or renal replacement therapy.

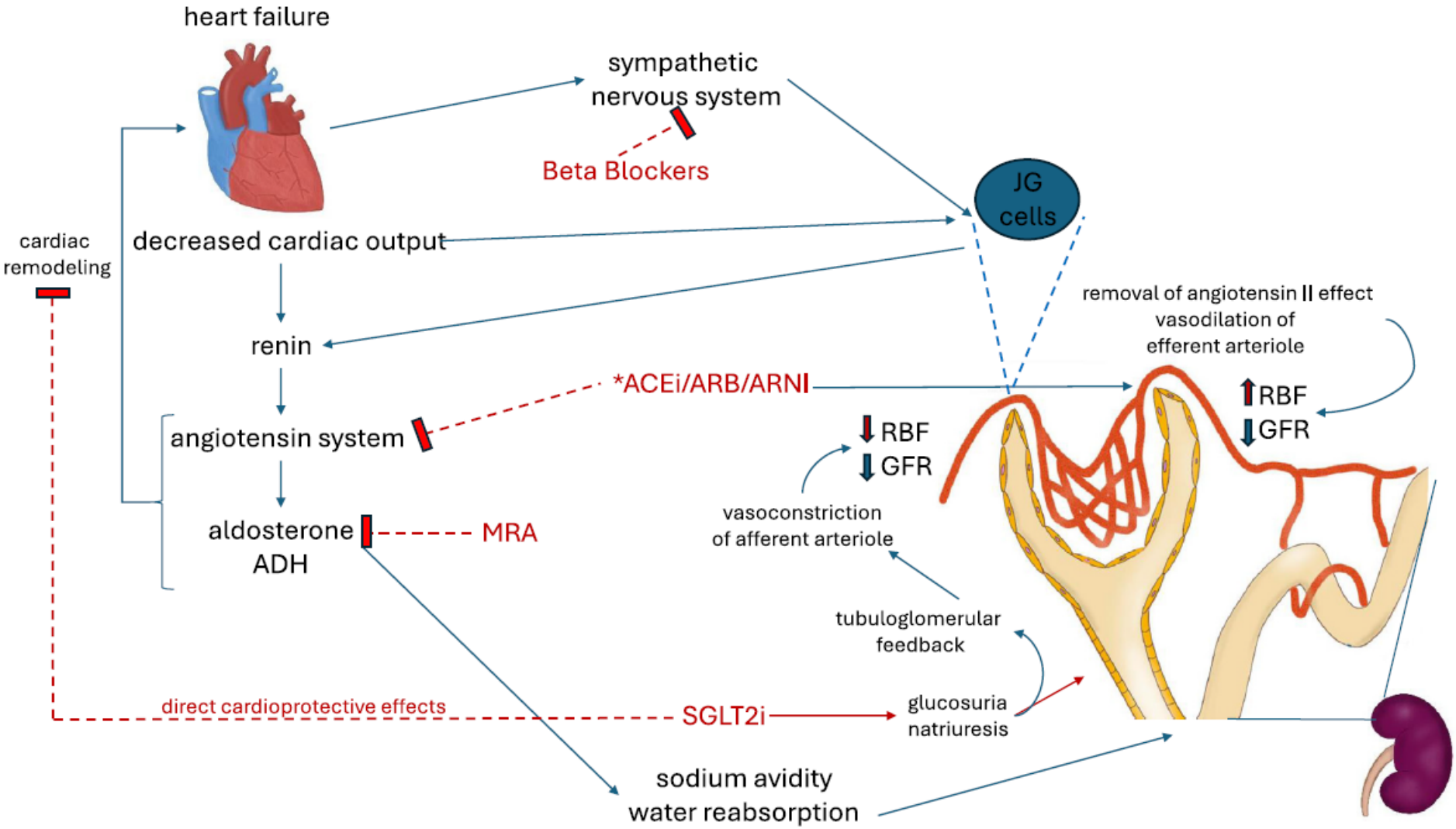
- Glucagon-like peptide receptor agonists has also recently garnered attention, especially in cases of HF with preserved EF with the obesity phenotype reduction of kidney events and cardiovascular death in patients with type 2 diabetes and CKD.

Table 2. Summary Table on Key Clinical Trials on Guideline Directed Medical Therapy for Heart Failure

Study, Year	Drug	Control	Population Enrolled	CV Outcome	*P* Value	Renal Function Exclusion
ARNIs						
PIONEER-HF, 2021	Sacubitril/valsartan	Enalapril	HFrEF	Time-averaged proportional change in NT-proBNP concentration from baseline through weeks 4 and 8: −46.7% vs. −25.3%	<0.001	–
PARADIGM-HF, 2014	Sacubitril/valsartan	Enalapril	HFrEF	CV mortality or HF hospitalization: 21.8% vs. 26.5%	<0.001	GFR <30
PARAMOUNT, 2012	Sacubitril/ valsartan (LC696)	Valsartan	HFrPEF	Change in NT-proBNP at 12 weeks vs valsartan; LCZ696/valsartan ratio, 0.77	0.005	GFR <30
β-Blockers						
MERIT-HF, 1999	Metoprolol	Placebo	HFrEF	All-cause mortality: 0.072 vs 0.11 per patient-year	<0.001	–
COPERNICUS, 2002	Carvedilol	Placebo	HFrEF	Annual mortality: 12.8% vs 19.7%	<0.001	–
MRA						
RALES, 1999	Spironolactone	Placebo	HFrEF	All-cause mortality: 35% vs 46%	<0.001	Cr >2.5
EMPHASIS-HF, 2011	Eplerenone	Placebo	HFrEF	CV death or HF hospitalization: 18.3% vs 25.9%	<0.001	GFR <30
EPHESUS, 2003	Eplerenone	Placebo	HFrEF	All-cause mortality: 19.8% vs 24.7%	0.008	Cr > 2.5
TOPCAT, 2014	Spironolactone	Placebo	HFpEF	CV mortality, aborted cardiac arrest, or HF hospitalization: 18.6% vs 20.4%	0.1	Cr >2.5 or GFR <30
Nonsteroidal MRAs						
FIDELIO-DKD, 2021	Finerenone	Placebo	NA	CV mortality, nonfatal MI, nonfatal stroke, or HF hospitalization[a]: 13.0% vs 14.8%	0.03	–
FIGARO-DKD, 2021	Finerenone	Placebo	NA	CV death, MI, stroke, hospitalization for HF: 12.4% vs 14.2%	0.03	GFR <25
FINEARTS-HF, 2024	Finerenone	Placebo	HFmrEF, HFpEF	Composite of worsening HF events (first or recurrent unplanned HF hospitalization or urgent visit) and CV death (14.9 vs 17.7 events per 100 patient-years)	0.007	GFR <25, serum K >5.0
ARBs						
Val HeFT, 2001	Valsartan	Placebo	HFrEF	All-cause mortality: 19.7% vs 19.4%	0.8	Cr >3.4
ACE inhibitors						
CONSENSUS, 1987	Enalapril	Placebo	NYHA class IV	6-month mortality: 26% vs 44%	0.002	Cr >3.4
SOLVD, 1991	Enalapril	Placebo	HFrEF	All-cause mortality: 35% vs 40%	0.007	Cr >2.0
SGLT2 inhibitors						
DAPA-HF, 2019	Dapagliflozin	Placebo	HFrEF	Worsening HF (hospitalization or urgent visit resulting in IV therapy for HF) or CV mortality: 16.3% vs 21.2%	<0.001	GFR <30
DELIVER, 2022	Dapagliflozin	Placebo	EF >40%	HF hospitalization, urgent HF visit, or CVD mortality: 16.4% vs 19.5%	<0.001	GFR <25
EMPEROR-PRESERVED, 2015	Empagliflozin	Placebo	EF > 40%	Death from cardiovascular causes or hospitalization for HF: 13.8% vs 17.1%	<0.001	GFR <20

(Continued)

GDMT OPTIMIZATION IN HF AND KIDNEY DISEASE



GDMT OPTIMIZATION IN HF AND KIDNEY DISEASE

HFrEF therapies	CKD 1 and 2	CKD 3	CKD 4	CKD 5
Beta Blocker	Strong	Strong	Limited	Absent
MRA	Strong	Strong	Limited	Absent
Non-steroidal MRA	Strong	Strong	Strong (up to eGFR> 25 cc/min)	Absent
ARNi	Strong	Strong	Limited	Absent
ACEi/ARB	Strong	Strong	Limited	Absent
Diuretics	Absent	Absent	Absent	Absent
SGLT2i	Strong	Strong	Strong (eGFR> 20 cc/min)	Limited

CHALLENGES IN GDMT OPTIMIZATION ESPECIALLY IN CKD

Patient Profile	65-year-old man
PMH	DM, CKD(G3aA3), HTN
PDH	furosemide 40 mg twice daily and metoprolol succinate and lisinopril 20 mg
Vital sign	T: 36.1C, PR:88, RR: 15, BP:100/57
PH/E	No JVP distension, No bilateral crackles
Lab Data	NA :136 mEq/L K: 5.3 mEq/L, CL:102 mEq/L, CR: 1.6 mg/dL (at baseline) SUN; 15 mg/dL,s NT-proBNP: 1500 pg/mL.
Echo	EF35%
Management	lisinopril was stopped, and the patient was referred to the nephrology service to help with GDMT optimization

CHALLENGES IN GDMT OPTIMIZATION ESPECIALLY IN CKD

Question 8: What is the next best step for this patient?

(a) Start spironolactone
(b) Increase the furosemide dose
(c) Add an SGLT2 inhibitor together with lisinopril
(d) Maintain deescalation of lisinopril
(e) Add metolazone 3 times per week

- Hyperkalemia is commonly one of the limiting adverse effects encountered when titrating GDMT in patients with HF and CKD (MRA and RAAS inh).

1. SGLT2 inhibitors reduced the risk of serious hyperkalemia.
2. Another alternative is switching to an ARN inh.
3. Potassium binder use can also be considered for GDMT maintenance in HF.

CHALLENGES IN GDMT OPTIMIZATION ESPECIALLY IN CKD

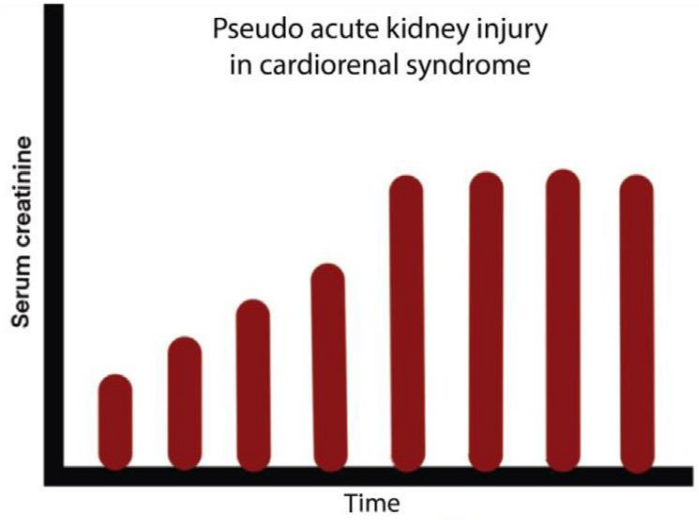
Patient Profile	45-year-old woman
PMH	DM, HTN, New HF
PDH	furosemide 40 mg/d and metoprolol succinate, isinopril 20 mg/d and empagliflozin 10 mg/d 2 weeks earlier.
PH/E	No JVP distension, No bilateral crackles, euvolemic
Lab Data	NA :136 mEq/L K: 4.5 mEq/L, CL:102 mEq/L, CR: 1.5 mg/dL (at baseline 1.2) SUN; 16 mg/dL,s NT-proBNP: 900 pg/mL (decreased from 1,400 pg/mL 2 weeks earlier).
Echo	EF35%

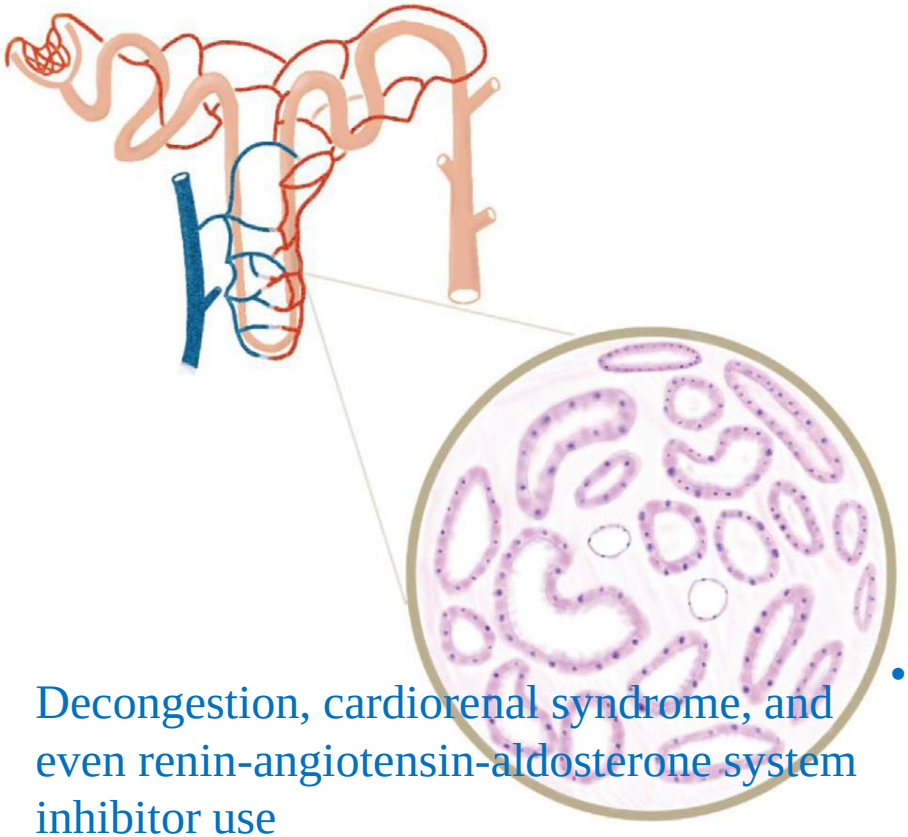
CHALLENGES IN GDMT OPTIMIZATION ESPECIALLY IN CKD

Question 9: What is the next best step for this patient?

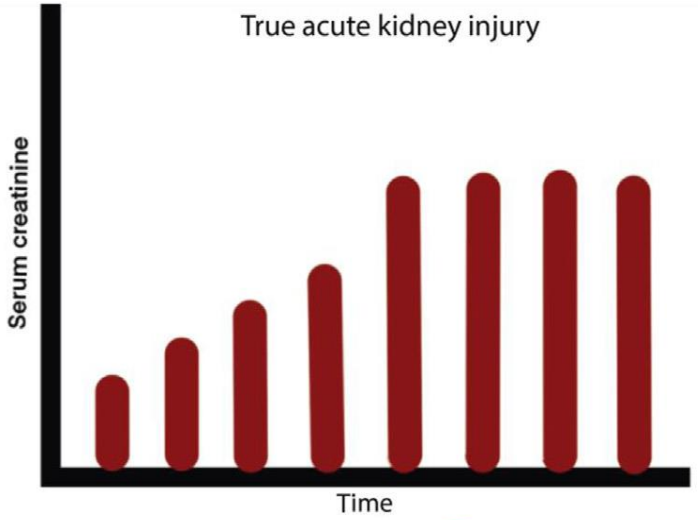
(a) Continue lisinopril and empagliflozin
(b) Stop lisinopril
(c) Switch lisinopril to valsartan
(d) Stop empagliflozin

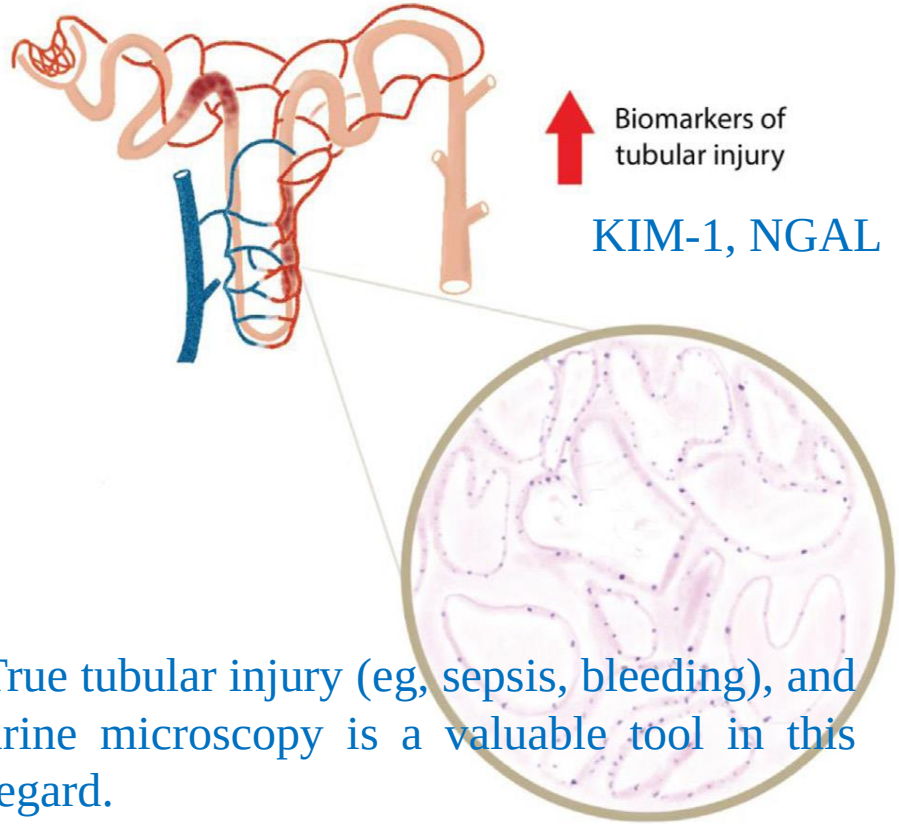
- Initiation of a RAAS inhibitor or SGLT2 inhibitor can be associated with fluctuations in serum creatinine of as much as 0.3 mg/dL or more within the first 2 weeks of initiation. Guidelines have recommended continuation if the eGFR decrease is <30% versus baseline.
- EMPA-KIDNEY trial 6% decrease in eGFR.
- Chronic slope of eGFR decline slowing of kidney disease progression with a relative difference of 50% (95% CI, 42%-58%).
- Improvement in cardiac and kidney outcomes





- Decongestion, cardiorenal syndrome, and even renin-angiotensin-aldosterone system inhibitor use





KIM-1, NGAL

- True tubular injury (eg, sepsis, bleeding), and urine microscopy is a valuable tool in this regard.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